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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
KIM, YOUNG J	
ART UNIT	PAPER NUMBER
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/08/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/655,762	CANTOR ET AL.	
	Examiner	Art Unit	
	Young J. Kim	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-8 and 10-14* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-8 and 10-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *2/2/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 18, 2006 has been entered.

Preliminary Remark

Claims 4 and 9 have been canceled.

Claims 10-14 are new.

Claims 1-3, 5-8, and 10-14 are pending and are under prosecution therefore.

It is been noted that claim 8 has been marked as being "currently amended." However, said claim does not have any markings showing of the changes made. Since the examiner was able to identify the changes without undue time, the amendment had been considered.

However, Applicants are clearly advised that all requirements under the new amendment practice must be followed so as to avoid a notice of informal or non-compliant notice (NINA).

Information Disclosure Statement

The IDS received on February 2, 2007 is acknowledged.

A signed copy of the PTO-1449 is enclosed herein.

Claim Rejections - 35 USC § 112

The rejection of claims 1-8 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter, made in the Office Action mailed on July 20, 2006 is withdrawn in view of the Amendment received on February 2, 2007.

Claim Rejections - 35 USC § 102

The rejection of claims 1, 3, and 5-7 under 35 U.S.C. 102(b) as being anticipated by Bunn et al. (U.S. Patent No. 5,213,961, issued May 25, 1993), made in the Office Action mailed on July 20, 2006 is withdrawn in view of the Amendment received on February 2, 2007. Specifically, Bunn et al. do not disclose a method of quantification involving mass spectrometry.

The rejection of claims 1, 3, and 6 under 35 U.S.C. 102(b) as being anticipated by Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref), made in the Office Action mailed on July 20, 2006 is withdrawn in view of the Amendment received on February 2, 2007. Specifically, Becker et al. do not disclose a method of quantification involving mass spectrometry.

Claim Rejections - 35 USC § 103

The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Bunn et al. (U.S. Patent No. 5,213,961, issued May 25, 1993) in view of Carroll et al. (U.S. Patent No. 5,906,744, issued May 25, 1999), made in the Office Action mailed on July 20, 2006 is withdrawn in view of the Amendment received on February 2, 2007. Specifically, Bunn et al. do not disclose a method of quantification involving mass spectrometry and Carroll et al. do not cure this deficiency.

The rejection of claim 2 under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref) in view of Carroll et al. (U.S. Patent No. 5,906,744, issued May 25, 1999), made in the Office Action mailed on July 20, 2006

is withdrawn in view of the Amendment received on February 2, 2007. Specifically, Becker et al. do not disclose a method of quantification involving mass spectrometry and Carroll et al. do not cure this deficiency.

The rejection of claim 4 rejected under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref) in view of Amexis et al. (PNAS, October 2001, vol. 98, no. 21, pages 12097-12102), made in the Office Action mailed on July 20, 2006 is withdrawn in view of the Amendment received on February 2, 2007, canceling the rejected claim.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 5, 7, and 8 under 35 U.S.C. 103(a) as being unpatentable over Becker et al. (Nucleic Acids Research, 1989, vol. 17, no. 22, pages 9437-9446; IDS ref) in view of Amexis et al. (PNAS, October 2001, vol. 98, no. 21, pages 12097-12102), made in the Office Action mailed on July 20, 2006 is maintained for the reasons already of record.

In addition, as Applicants included the limitation of claim 4 (which was previously rejected) into base claim 1, claim 1 is rejected herein as being necessitated by the Amendment received on February 2, 2007. In addition, claims 2, 3, 6, and 10-14 are rejected herein, as being necessitated by said Amendment.

Applicants' arguments presented in said Amendment received on February 2, 2007 have been fully considered but they are not found persuasive for the reasons set forth in the, "Response to Arguments," section.

The Rejection:

Becker et al. disclose a method of measuring the amount of target nucleic acid sequence in a biological sample, comprising the steps:

a) preparing a sample by adding known amount of a standard nucleic acid, wherein said standard nucleic acid has a single nucleotide sequence difference from the target nucleic acid (page 9437, bottom paragraph, in the phrase, "mutated cDNA serves as internal standard"; and page 9438, 2nd paragraph; Figure 1);

b) amplifying the sample of step (a) (see Figure 1, via PCR);

c) using a further method to enhance the difference between the standard and the target nucleic acid sequence at the site resulting in enhanced products so that the difference created by the at least one base between the standard and the target nucleic acid can be detected (the digestion step of Figure 1 which enhances the difference between the standard and the target nucleic acid);

d) quantifying the enhanced products of step (c) by measuring the ratio of the amplified target nucleic acid to the amplified standard nucleic acid to measure the amount of target nucleic acid present in the sample (Figure 2; page 9442, bottom paragraph).

The target nucleic acid is mRNA (page 9437, 2nd paragraph).

The enhancement is achieved via an enzyme which specifically cleaves at the site of differentiation (*Eco*RI digesion; page 9442, bottom paragraph).

Becker et al. do not employ mass spectrometry in their quantification method (claims 4 and 8).

Becker et al. do not explicitly disclose a method of performing primer extension at the site of differentiation (claim 5), or allele-specific hybridization at the site of differentiation (claim 7).

Becker et al. do not explicitly disclose that the method measures the amount of at least 5, 10, 25, or 50 target nucleic acid sequences using at least 5, 10, 25, or 50 standard nucleic acids, respectively (claims 10-13).

Amexis et al. disclose a method of quantifying a target nucleic acid in a sample, in particular, RNA virus (thus infectious agent), wherein the method comprises the steps of:

a) amplification of a target nucleic acid with a pair of primers (Figure 1B; page 12098, 2nd column, 3rd paragraph);

b) amplifying the amplified product with MassExtend primers which is specific for a point mutation (Figure 1B; page 12098, 2nd column, 3rd paragraph (middle)); and

c) detecting and quantifying the amplified products (Figure 1B; page 12098, 2nd column, 3rd paragraph (bottom); Abstract; page 12098, 1st column, 3rd paragraph).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine the teachings of Becker et al. and with the teachings of Amexis et al., thereby arriving at the claimed invention for the following reasons.

The method employed by Becker et al., which is drawn to the amplifying the target nucleic acid and the standard nucleic acid (which contains a single nucleotide mutation) via use of primers which flank the target nucleic acid region, employs more than a decade old technique – that is – restriction digest, electorphoresis, followed by the radiolabeled (^{32}P) quantitation method.

Thus, one of ordinary skill in the art at the time the invention was made would have been motivated to employ a non-radioactive method of accurately quantitating the target nucleic acid, such as MALDI-TOF, thereby arriving at the claimed invention.

One of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success at combining the teachings since methods of quantification employing mass spectrometry, such as SNuPE (single nucleotide primer extension), have been well-established. Given the fact that Amexis et al. amplify a known target nucleic acid sequence via use of a flanking primer pairs, followed by the mutation-specific primer extension, one of ordinary skill in the art would have recognized that the amplification products of Becker et al., would have served equally well for the mutation-specific primer extension, which would have been necessary for the subsequent mass spectrometric analysis.

Therefore, the invention as claimed is *prima facie* obvious over the cited references.

Response to Arguments:

Applicants contend that based on the teachings of Becker et al., one of ordinary skill in the art would have been motivated to look for teachings of labeling, such as fluorescent or enzymatic labels, that would have been directly applicable to the gel electrophoretic method taught by Becker et al. (page 7, 5th paragraph, Response).

Applicants state that since there is nothing in Alexis that would direct one of ordinary skill in the art to choose to combine it with a totally different type of method, particularly a method that would require additional steps, one of ordinary skill in the art would not have been motivated to combine the teachings (page 7, 5th paragraph, Response).

Applicants conclude that there would be no motivation for one of ordinary skill the art to combine the teachings of Amexis et al. because one of ordinary skill in the art would not have been motivated to make the system more complicated than that which was already disclosed by Becker et al. (page 7, 5th paragraph, Response).

Applicants' arguments are noted, but are not found to be persuasive because Applicants' reasoning is fundamentally flawed.

Applicants state that one of ordinary skill in the art at the time the invention was made would have only been motivated to employ other means of labeling the nucleic acids, such as fluorescent or enzyme-mediated processes, for the purpose of quantifying the nucleic acid, when viewing the teachings of Becker et al.

Were Applicants' assertions to be true of a one of ordinary skill in the art, the art of nucleic acid sequencing via mass-spectrometric method would never have been invented, since, as Applicants' put it, it would require more steps, thereby making the sequencing method, "more complicated."

However, it is a fact that there clearly exists methods of sequencing or, determining polymorphic nucleotides, wherein the method relies on techniques other than the traditional method of sequencing via fluorescently tagged ddNTPs, including mass spectrometry.

In particular, the reference published by Amexis et al. (PNAS, 2001, vol. 98, no. 21, pages 12097-12102), evidences this fact:

> "Matrix-assisted laser desorption/ionization time of flight (MALDI-TOF) mass spectrometry is now being used for analysis of nucleic acids...including genetic variations such as microsatellites, insertion/deletions, and especially single-nucleotide polymorphisms (SNPs)...The output data are a measure of intrinsic characteristic of the DNA products being studied...*no direct measurement of the products is involved, as with fluorescent or radiolabel tagging*... The ability to resolve oligonucleotides varying in mass by less than a single nucleotide makes MALDI-TOF mass spectrometry an excellent platform for SNP and mutant analysis." (page 12098, 1st column, 2nd paragraph)

The artisans also compare the sensitivity between MAPREC, which involves PCR reaction, restriction treatment, followed by gel analysis (i.e., running the gel), and MALDI-TOF (page 12101, 2nd column, 2nd paragraph), indicating that while the two assays are as sensitive, but clearly states that

MAPREC is, "limited because it is a relatively time-consuming procedure that cannot be easily scaled up either for processing of multiple samples or analysis of multiple genetic markers..."

While Applicants' concentrate on the purportedly "additional steps" that may be required for implementing MALDI-TOF for quantitating the PCR products, Applicants do not factor in the benefit said one of ordinary skill in the art would have gleaned from employing the method disclosed by Amexis et al.

Clearly, one of ordinary skill in the art at the time the invention was made would have recognized the benefit of employing the non-radioactive, more time-efficient way of quantifying target nucleic acids, rather than employing the biohazardous, radioactive labels, as well as running an electrophoretic gel for quantitation.

Finally, Applicants argue that since the method of Becker et al. was for a single target nucleic acid quantification, one of ordinary skill in the art at the time the invention was made would not have been motivated to arrive at the claimed invention of quantitating at least two target nucleic acids or more.

This arguments is not found persuasive.

It is a fact, that multiplex amplification of different target nucleic acids has been well established, for the well known benefit of simultaneously amplifying a plurality of targets simultaneously, resulting not only in efficiency in time, but also with respect to reagent costs.

For Applicants' to argue that an ordinarily skilled artisan at the time the invention was not aware of such techniques (which would be over a decade from the time Becker's invention was disclosed) or would not have been motivated to apply the teaching of Becker et al. for amplifying more than a single target nucleic acid would severely undermine the skill of said ordinarily skilled artisan.

In addition, Amexis et al. was clear in that the adoption of MALDI-TOF would allow one of ordinary skill in the art to process a plurality of samples or multiple markers (see page 12101), giving the one of ordinary skill in the art a more than a reasonable expectation of success at arriving at the claimed invention.

For the above reasons, Applicants' arguments are not found persuasive and the rejection is maintained for the reasons already of record.

Conclusion

No claims are allowed.

Inquiries

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Young J. Kim whose telephone number is (571) 272-0785. The Examiner is on flex-time schedule and can best be reached from 8:30 a.m. to 4:30 p.m (M-W and F). The Examiner can also be reached via e-mail to Young.Kim@uspto.gov. However, the office cannot guarantee security through the e-mail system nor should official papers be transmitted through this route.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Dr. Gary Benzion, can be reached at (571) 272-0782.

Papers related to this application may be submitted to Art Unit 1637 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant does submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office. All official documents must be sent

to the Official Tech Center Fax number: (571) 273-8300. For Unofficial documents, faxes can be sent directly to the Examiner at (571) 273-0785. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Young J. Kim
Primary Examiner
Art Unit 1637
3/1/2007

YOUNG J. KIM
PRIMARY EXAMINER

YJK